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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/975,899
Filing Date: October 12, 2001
Appellant(s): GOETZ ET AL.

Benjamin Aaron Adler
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed January 12, 2005.

(1) Real Party of Interest.

A statement identifying the real party of interest in contained in the Brief.

(2) Related Appeals and Interferences Identified.

A statement identifying that no related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the Brief.

(3) Status of Claims

The statement of the status of the claims contained in the Brief is incorrect.
A correct statement of the status of the claims is as follows:
Claims 1-5 and 7 have been canceled.
Pending claim 6 is being appealed.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the Brief is correct.

(5) Summary of Invention

The summary of invention contained in the Brief is correct.

(6) Grounds of Rejection to be reviewed on Appeal

The following ground of rejection is applicable to the appealed claim:

Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hallahan (US Patent NO: 6,159,443) in view of WO 98/53852 , the admissions of the prior art disclosed in the specification [on pages 4, lines 3-20 ; page 5, lines 1-5; and 10, lines 12-20], Mastrobattista et al.,(Biochim. Biophys. Acta, 1999, 1419, 353-363) and Patel et al (FASEB 1998, Vol.12 pages 1447-1454).

US Patent '443 teaches a method of treating cancer , the method comprising steps of exposing a target tissue or organ to the ionizing radiation and administering P-selectin antibody labeled delivery vehicle that carry active agent to the tumors (see entire document, Abstract , column 6, lines 5-30 and column 13, lines 24-30 in particular). US Patent '443 teaches radiation –induced increase in P-selectin in irradiated tumor and that the present invention contemplate the selective targeting of tumors by delivering radiation to target tumors and using a delivery vehicles which bind to P-selectin. The use of radiation to control cellular adhesion molecules, such as P- selectin, is a unique approach to the treatment of tumors (see column 6, lines 5-15 in particular). US Patent '443 teaches that delivery vehicle is a biodegradable particles bearing antibodies that specifically bind to a P-selectin (column 7-8 in particular). US Patent '443 teaches biodegradable particle such as microspheres or liposomes as delivery vehicles (see column 7, lines 45-65 in particular). It is noted that the specification as filed disclosed liposomes as one of the examples of biodegradable particle (see page 11 lines 3-20 of the instant Specification in particular). US Patent 443 explicitly teaches that following irradiation P-selecting is translocated to the cell membrane of endothelial cells (see column 24, lines 10-30 in particular). US Patent 443 teaches that radiation –induced translocation of P-selecting to the cell membrane was complete at 30 min. after irradiation (see column 26, lines 40-60 in

particular). Moreover, the specification clearly disclosed that it was known at the time the invention was made that P-selectin translocated to the cell membrane of endothelial cells within 30 minutes post irradiation (see page 9, lines 3-10 of the instant Specification in particular) . Therefore it would have been obvious to one of ordinary skill in the art at the time the invention was made to conclude that P-selectin would be expressed in endothelial cells following irradiatation of tumors.

The claimed invention differs from the reference teaching in that US Patent '443 does not teach a particle of biodegradable polymers or PEGylated copolymers comprising antibodies that binds to ICAM-1.

WO' 852 teaches the role of several cell adhesion molecules in the radiation-mediated treatment of tumors (see entire document, page 4, lines 17-20 in particular). WO'852 teaches that exposure tissue to irradiation causes an increase in expression of several cell adhesion molecules (CAM) including ELAM-1, E-selectin and ICAM-1, and P-selectin in endothelial cells (see entire document, page 2, lines 15-25 and page 3, lines 1-10, page 16, lines 5-25, page 55, lines 20-25 in particular). WO' 852 teaches the invention requires the overexpression cell adhesion molecules , for example P-selectin or ICAM-1, in endothelial cells caused by ionizing radiation, which then allows said cell adhesion molecules to be targeted using specific binding composition and selected agents (see page 6, lines 20-26 and page 15, line 4-25, page 16, lines 5-20 in particular). WO' 852 teaches that CAM- targeting components is antibody (see page 8, lines 13-18 in particular).

The known fact disclosed in the specification on pages 4, lines 3-20 ; 5, lines 1-5; and 10, lines 12-20 teaches that it has been known for over 15 years that exposure of normal and diseased tissue to irradiation causes an increase leukocyte infiltration and that the key component of this process is the adhesion of leukocytes to the microvascular endothelium. In response to biochemical stimuli the endothelium become activated and increases its expression of receptors of several cellular adhesion molecule including E-selectin, P-selectin and ICAM-1.

Mastrobattista et al. teach biomolecular carrier, bearing anti ICAM-1 antibodies (see entire document, Abstract in particular). It is noted that Mastrobattista et al.. clearly stated that biomolecular carrier, bearing anti ICAM-1 antibodies can be effectively used to delivery drugs to the sites where the expression of ICAM-1 is increased (see Abstract in particular).

Patel et al., teaches a generation a particle of biodegradable polymer or PEGylated copolymer as a new type of drug carrier (see entire document, Abstract in particular). Patel et al., teaches that one of the advantage of using said particles is that they are not rapidly removed from the circulation (see page 1448 in particular).

It is clear that both the prior art and claimed method administer the same treatment i.e. irradiating a cancerous target tissue or organ and further administering to said individual a biodegradable particle comprising an antibody that binds to an cellular adhesion molecules expression of which is increases after exposure of said tissue or organ to irradiation, to the same group of patients (cancer patients) to achieve the same results. Thus it would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of WO'852, Mastrobattista et al., Patel et al., and Appellant's admissions of prior art set forth in the specification [on page 4, 3-20 ; page 5, lines 1-5; and 10, lines 12-20]to those of US Patent ' 443 and substitute biomolecular carrier bearing antibodies to one species of cellular adhesion molecule i.e. P-selectin to another type of particle of biodegradable polymers or PEGylated copolymers carrier bearing antibodies to another species of cellular adhesion molecule i.e. ICAM-1 . The expression of any one of said cell adhesion molecules would be enhanced in target tissue after irradiation, as taught WO'852 and the known prior art disclosed in the Specification. Said biodegradable polymers or PEGylated copolymers carrier bearing antibodies to ICAM-1 can be used in the method of treating a cancer taught by US Patent '443.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so, because it has been known for over 15 years that exposure of normal and diseased tissue to irradiation causes an increase leukocyte infiltration and that the key component of this

process is the adhesion of leukocytes to the microvascular endothelium, as taught by the known fact disclosed in the specification on pages 4, lines 3-20 and exposure tissue to irradiation causes an increase in expression of several species of cell adhesion molecules including ELAM-1, E-selectin and ICAM-1, in endothelial cells, as taught by the WO'852 and P-selectin labeled delivery vehicle was used to delivery drugs to target cancer tissue or organ where the expression of this cell adhesion molecule was increased by exposure said tissue or organ to irradiation, as taught by US Patent '433 and biomolecular carrier, bearing antibodies to another cell adhesion molecules ICAM-1 effectively used to delivery drugs to the sites where the expression of ICAM-1 is increase, as taught by Mastrobattista et al. In addition, using a particle of biodegradable polymer or PEGylated copolymer as a new type of drug carrier is more advantage because they are not rapidly removed from the circulation as taught by Patel et al.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

(7) Response to Argument

At overlapping pages 8 -9 of the Brief, Appellant asserts that the cited references do not teach in vivo targeting of ICAM-1 expressed on the surface of endothelial cells. Hallahan only teaches P- selectin which is localized to the vascular lumen and not on the vascular endothelial cell surface in irradiated tumors in vivo. Mastrobattista et al., only teaches the uses of anti-ICAM-1 immunoliposomes to target bronchial epithelial cells *in virto*. In the absence of actual experimentation it is not clear whether biomolecular carriers bearing anti-ICAM-1 antibody administered in vivo will be diverted away from target tissue and bind to other ICAM-1 expressing cells. At page 11 of the Brief, Appellant further asserts that whether

anti-ICAM-1 antibodies can be used to target tumor tissue in vivo has to be determined by actual experimentation.

At page 13 of the Brief, Appellant asserts that even the prior art teaches that P-selectin and ICAM-1 are overexpressed when tissue is irradiated, one cannot equate targeting P-selectin with targeting ICAM-1.

At page 14 of the Brief, Appellant asserts that any teaching or suggestion or motivation found in Pater at al., to substitute biodegradable polymers for the liposomes does not overcome the problem specificity of targeting ICAM-1 in vivo, that have to be determined through empirical experimentation.

Appellant have traversed the primary and the secondary references pointing to the differences between the claims and the disclosure in each reference. Appellant is respectfully reminded that the rejection is under 35 USC103 and that unobviousness cannot be established by attacking the references individually when the rejection is based on the combination of the references. see In re Keller, 642 F.2d 4B, 208 USPQ 871, 882 (CCPA 1981) See MPEP 2145. This Appellant has not done, but rather argues the references individually and not their combination. One cannot show non-obviousness by attacking references individually where the rejections are based on a combination of references. In re Young 403 F.2d 759, 150 USPQ 725 (CCPA 1968).

The examiner disagrees with the Appellant's statement that " Hallahan only teaches P- selectin which is localized to the vascular lumen and not on the vascular endothelial cell surface in irradiated tumors in vivo". Both prior art references of Hallahan i.e. US Patent '443 and WO'852 clearly stated that P-selectin is expressed in endothelial cells following by irradiation. Appellant's attention is respectively drawn to columns 24, lines 10-30 and column 26, lines 10-30 of US Patent '443 and page 15, lines 4-25 of WO'852. US Patent '443 explicitly teaches that following irradiation P-selecting is translocated to the cell membrane of endothelial cells. US Patent '443 further teaches that radiation –induced translocation of P-selectin to the cell membrane of endothelial cells was complete at 30 min. after irradiation . WO'852 explicitly teaches that endothelial cells line the lumen of blood vessels and cell adhesion molecules (CAM) expressed **on their surface** represent a potential target for "site directed" pharmaceuticals

Moreover, in Example I WO'852 explicitly teaches that expression of E-selectin and ICAM increased in endothelial cells following irradiation. In other words, based on teaching WO'852 one skill in the art would have immediately recognized that irradiation results in overexpression of cell adhesion molecules on an endothelial cells of irradiated tissue or organ. In addition, Appellant had already acknowledge that the combined teaching of Hallahan, WO'852 and Mastrobattista et al ., would suggest to or motivate one of ordinary skill in the art to administer an anti-ICAM-1 immunoliposone comprising an active agent to irradiated tumor tissue (see Appellant's arguments, filed on 07/22/04, page 10, end of first paragraph in particular).

US Patent '443 teaches a method of treating cancer , the method comprising steps of exposing a target tissue or organ to the ionizing radiation and administering P-selectin antibody labeled delivery vehicle that carry active agent to the tumors (see entire document, Abstract , column 6, lines 5-30 and column 13, lines 24-30 in particular). US Patent '443 teaches radiation –induced increase in P-selectin in irradiated tumor and that the present invention contemplate the selective targeting of tumors by delivering radiation to target tumors and using a delivery vehicles which bind to P-selectin. The use of radiation to control cellular adhesion molecules, such as P- selectin, is a unique approach to the treatment of tumors (see column 6, lines 5-15 in particular). US Patent '443 teaches that delivery vehicle is a biodegradable particles bearing antibodies that specifically bind to a P-selectin (column 7-8 in particular). US Patent '443 teaches biodegradable particle such as microspheres or liposomes as delivery vehicles (see column 7, lines 45-65 in particular). It is noted that the specification as filed disclosed liposomes as one of the examples of biodegradable particle (see page 11 lines 3-20 of the instant Specification in particular).

WO' 852 teaches the role of several cell adhesion molecules in the radiation-mediated treatment of tumors (see entire document, page 4, lines 17-20 in particular). WO'852 teaches that exposure tissue to irradiation causes an increase in expression of several cell adhesion molecules (CAM) including ELAM-1, E-selectin and ICAM-1, and P-selectin in endothelial cells (see entire document, page 2, lines 15-25 and page 3, lines 1-10, page 16, lines 5-25, page

55, lines 20-25 in particular). WO'852 explicitly teaches that endothelial cells line the lumen of blood vessels and cell adhesion molecules (CAM) expressed **on their surface** represent a potential target for "site directed" pharmaceuticals. WO' 852 teaches the invention requires the overexpression cell adhesion molecules , for example P-selectin or ICAM-1, in endothelial cells caused by ionizing radiation, which then allows said cell adhesion molecules to be targeted using specific binding composition and selected agents (see page 6, lines 20-26 and page 15, line 4-25, page 16, lines 5-20 in particular). WO' 852 teaches that CAM- targeting components is antibody (see page 8, lines 13-18 in particular). Moreover, in Example I, WO'852 explicitly teaches that expression of E-selectin and ICAM increased in endothelial cells following irradiation.

The admitted prior art disclosed in the specification on pages 4, lines 3-20 ; 5, lines 1-5; and 10, lines 12-20 teaches that it has been known for over 15 years that exposure of normal and diseased tissue to irradiation causes an increase leukocyte infiltration and that the key component of this process is the adhesion of leukocytes to the microvascular endothelium. In response to biochemical stimuli the endothelium become activated and increases its expression of receptors of several cellular adhesion molecule including E-selectin, P-selectin and ICAM-1.

Mastrobattista et al. teach biomolecular carrier, bearing anti ICAM-1 antibodies (see entire document, Abstract in particular).

Appellant's further asserts that Mastrobattista et al. , only teaches the uses of anti-ICAM-1 immunoliposomes to target bronchial epithelial cells *in vitro* and that whether anti-ICAM-1 antibodies can be used to target tumor tissue *in vivo* has to be determined by actual experimentation. It is noted that Mastrobattista et al.. clearly stated that biomolecular carrier, bearing anti ICAM-1 antibodies can be effectively used to delivery drugs to the sites where the expression of ICAM-1 is increased (see Abstract in particular). In other words , Mastrobattista et al., clearly indicated that anti-ICAM-1 immunoliposomes can be used for in vivo targeting the sited where the expression of ICAM-1 is increase.

Moreover, the Examiner disagrees with the Appellant's statement that in view of the *in vitro* experiments taught Mastrobattista et al., it would not be obvious to one skill in the art to successfully target ICAM-1 expressing cells *in vivo.*). As has been discussed supra , it is the Examiner position that Mastrobattista et al., clearly indicated that anti-ICAM-1 immunoliposomes can be used for *in vivo* targeting the sited where the expression of ICAM-1 is increase. In addition, US Patent'433 explicitly teaches that *in vitro* endothelial model provides a means to study direct effects of ionizing radiation on expression of CAM, for example P-selectin, the endothelial cells *in vivo* (see co;umn 26, lines 50-60 in particular). In other words , US Patent '433 teaches that it would have been obvious to one skill in the art to conduct *in vivo* studies based on the successful *in vitro* data. It is well settled that specific statements in the references themselves which would spell out the claimed invention are not necessary to show obviousness, since questions of obviousness involves not only what references expressly teach, but what they would collectively suggest to one of ordinary skill in the art. See CTS Com. v. Electro Materials Corp. of America 202 USPQ 22 (DC SINY); and In re Burckel 201 USPQ 67 (CCPA). In the instant case the prior art teaches **the successful *in vivo*** targeting of a biodegradable particle comprising an antibody to P-selectin, to one species of cellular adhesion molecules (CAMs) expression of which is increases after exposure of said tissue or organ to irradiation. It is clear that both the prior art and claimed method administer the same treatment i.e. irradiating a cancerous target tissue or organ and further administering to said individual a biodegradable particle comprising an antibody that binds to an cellular adhesion molecules expression of which is increases after exposure of said tissue or organ to irradiation, to the same group of patients (cancer patients) to achieve the same results. In addition, Patel et al., teaches a generation a particle of biodegradable polymer or PEGylated copolymer as a new type of drug carrier (see entire document, Abstract in particular). Patel et al., teaches that one of the advantage of using said particles is that they are not rapidly removed from the circulation (see page 1448 in particular). Thus, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of prior art and substitute biodegradable particle comprising antibody to one species of cellular adhesion molecule i.e. P-selectin with biodegradable particle comprising antibody to another

species of cellular adhesion molecule i.e. ICAM-1, expression of which on endothelial cells also increases following irradiation.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so, because it has been known for over 15 years that exposure of normal and diseased tissue to irradiation causes an increase leukocyte infiltration and that the key component of this process is the adhesion of leukocytes to the microvascular endothelium, as taught by the known fact disclosed in the specification on pages 4, lines 3-20 and exposure tissue to irradiation causes an increase in expression of several species of cell adhesion molecules including ELAM-1, E-selectin , P-selectin and ICAM-1, in endothelial cells, as taught by the WO'852. Also P-selectin labeled delivery vehicle was used to delivery drugs to target cancer tissue or organ where the expression of this cell adhesion molecule was increased by exposure said tissue or organ to irradiation, as taught by US Patent '433 and biomolecular carrier, bearing antibodies to another cell adhesion molecules ICAM-1 effectively used to delivery drugs to the sites where the expression of ICAM-1 is increase, as taught by Mastrobattista et al. In addition, using a particle of biodegradable polymer or PEGylated copolymer as a new type of drug carrier is more advantageous because they are not rapidly removed from the circulation as taught by Patel et al.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Evidence appendix

1. US Patent 6,159443
2. WO 98/53852
3. Mastrobattista et al., Biochem, Biophys Acta, 1999, v.1419, pages 353-363.
4. Patel et al., FASEB, 1998, v.12, pages 1447-1454.

For the above reasons, it is believed that the rejections should be sustained.

Respectively submitted,

Michail Belyavskyi, Ph.D
Art Unit 1644
April 4, 2005

Conferees

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